REMARKS

The Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the claims

Claims 1-28 were previously canceled without disclaimer or prejudice thereof. Claims 29-64 are requested to be canceled in this paper without disclaimer or prejudice thereof.

Claims 65-72 are being added. The new claims add no new matter and exemplary support for the new claims can be found throughout the specification, for example, as shown in the table below.

New Claim	Exemplary Support
65	claim 29; page 3, line 28 to page 4 line 14; page 7, lines 10-13; page 15, lines 9-11
66	Page 6, lines 1-7; page 12, lines 8-14; examples 1 and 11
67, 68	Claim 31
69	Page 1, lines 21-31, continuing to page 2, lines 1-7; page 13, line 27; page 14 line 21.
70	Examples 1 and 11
71, 72	Claim 31

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 65-72 are now pending in this application.

II. Objections to the specification

The specification is objected to because "page 41, line 10 contains embedded hyperlinks or other forms of browser-executable code," and page 38, lines 10-25 describe Figure 8, however, "there is no corresponding Figure 8 in the drawings." (Office Action at page 3).

The specification has been amended to omit reference to the embedded hyperlinks or other forms of browser-executable code and to Figure 8. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

III. Claim rejection – 35 U.S.C. § 112, second paragraph

Claims 29-31 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Specifically, the office action asserts that the claims allegedly "omit essential steps," the phrase "the expression levels, ligand or nucleic acid" recited in claim 31 lacks sufficient antecedent basis, and that "claim 29 fails to specify whether 'the expression level of a peptide or polypeptide' determined in the mother, father or the fetus is correlated to preeclampsia." (Office Action at page 3). The Applicants respectfully traverse the rejection.

Without conceding to the correctness of the Office Action assertions and solely to expedite prosecution, claims 29-31 have been canceled, and new claims 65-72 comply with the requirements of 35 U.S.C. § 112, second paragraph, for at least the reasons provided below.

A. The claims omit essential steps

The Office Action asserts that the method claims fail to include 1) a contacting step for the sample and necessary assay reagents; 2) a detection step in which the reaction is quantified or visualized; and 3) a correlation step describing how results allow for a determination. (Office Action at page 3). The Office Action continues, asserting that no controls are set, and it is not clear whether and increase or a decrease in ADAM 12 is indicative of disease. (Id.)

New independent claims 65 and 69 recite the steps of obtaining a sample, determining the amount of a marker in the sample, comparing the measured amount of the marker with a reference amount and establishing a diagnosis based on the result of the comparison. The claim also makes clear that a higher amount of detected target as compared to the reference amount is indicative of preeclampsia or an increased risk of eclampsia, pregnancy induced hypertension, HELLP syndrome and intrauterine growth retardation. Thus, a sample and a control, detection and correlation steps and indication of disease are recited in the claims. The Applicants respectfully contend that the additional step of contacting the sample with the necessary reagents as suggested by the Examiner is unnecessary. The step of determining the amount of a marker inherently requires such a contacting step. Therefore, a contacting step need not be mentioned explicitly. Additionally, new claims 65 and 69 specify that the sample is obtained from a pregnant woman in the second or third trimester of pregnancy.

Thus, the reasons for the rejection are obviated. New claims 65-72 meet the requirements of 35 U.S.C. § 112, second paragraph, and reconsideration and withdrawal of the rejection is respectfully requested.

B. The phrase "expression level, ligand or nucleic acid" lacks antecedent basis

The Office Action asserts that the phrase "expression level, ligand or nucleic acid" as recited in claim 31 lacks antecedent basis. (Office Action at page 3). Claim 31 has been canceled, thereby obviating the rejection, and new claims 65-72 do not include this language.

Accordingly new claims 65-72 meet the requirements of 35 U.S.C. § 112, second paragraph, and reconsideration and withdrawal of the rejection is respectfully requested.

C. Claim 29 allegedly fails to specify the subject from which the sample is derived

Claim 29 is allegedly indefinite "because it fails to specify whether 'the expression level of a peptide or a polypeptide' determined in the mother, father or the fetus is correlated to preeclampsia." Claim 29 has been canceled, thereby obviating the rejection, and new claims 65-72 recite "obtaining a sample from a woman in the second or third trimester of pregnancy."

Accordingly new claims 65-72 meet the requirements of 35 U.S.C. § 112, second paragraph, and reconsideration and withdrawal of the rejection is respectfully requested.

IV. Claim rejection – 35 U.S.C. § 112, first paragraph, enablement

Claims 29-31 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. Specifically, the Office Action asserts that while the specification is enabling for "a method of diagnosing preeclampsia comprising (a) obtaining a serum sample for a pregnant women in the late 2nd and early 3rd trimester, (b) contacting samples from pregnant women with anti-ADAM 12-S (SEQ ID NO: 4) antibodies and (c) compare the level of ADAM 12-S in said serum sample to a gestational age-matched serum obtained from healthy women," the specification does not provide enablement for the diagnosis of a disease selected from the group consisting of preeclampsia, eclampsia, pregnancy-induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, and gestational diabetes by determining the expression level of either SEQ ID NO: 2 (ADAM 12-L) or SEQ ID NO: 4 (ADAM 12-S). (Office Action at page 4). The Applicants respectfully traverse this ground for rejection.

Without conceding to the correctness of the Office Action assertion and solely to expedite prosecution, claims 29-31 have been canceled thereby obviating the rejection with respect to these claims. New claims 65-72 meet the enablement requirements of 35 U.S.C. § 112, first paragraph, for at least the following reasons.

A. Claimed diseases and conditions

New claim 65 relates to a method for diagnosing preeclampsia, while new claim 69 relates to a method for diagnosing a patient at increased risk for eclampsia, pregnancy induced hypertension, HELLP syndrome, and intrauterine growth retardation.

As noted in the Office Action, methods for diagnosing preeclampsia are enabled by the specification (Office Action at page 4).

And, contrary to the Office Action assertions, a patient at increased risk of eclampsia, pregnancy induced hypertension, HELLP syndrome, and intrauterine growth retardation can be diagnosed using the claimed methods. As described in the specification, each of these diseases, eclampsia, pregnancy induced hypertension, HELLP syndrome, and intrauterine growth retardation is associated with or is known to be a possible complication of preeclampsia (*see e.g.*, Specification at page 1, lines 21-33; page 2, lines 5-7). Moreover, the assertions in the specification are supported by well-known references. For example, according to the ACOG practice bulletin, severe preeclampsia is associated with HELLP syndrome and fetal growth restriction (EXHIBIT A; America Family Physician Practice Guidelines –AGOG Practice Bulletin on Diagnosing and Managing Preeclampisa and Eclampsia, July 15, 2002; available at http://www.aafp.org/afp/2002715/practice.html). Similarly, Hofmeyr *et al.* describes HELLP syndrome as a possible complication of preeclampsia (EXHIBIT B; Hofmeyr *et al.* BMC Medicine, 2009 (7)11; available at http://www.biomedcentral.com/1741-7015/7/11), and the Merck Manual indicates that high blood pressure, HELLP syndrome and fetal growth restriction are associated with preeclampsia (EXHIBIT C; available at http://www.merck.com/mmpe/sec18/ch263/ch263j.html). Accordingly, a method for diagnosing preeclampsia also enables a method for diagnosing a patient at increased risk for hypertension, HELLP syndrome, and intrauterine growth retardation.

B. ADAM 12-L and SEQ ID NO: 8 as markers for preeclampsia and related diseases

The Office Action asserts that "ADAM 12-L is a membrane-bound protein, and the skilled…[artisan] would not expect to see the membrane-bound ADAM 12-L in any body fluid including sera," and that the specification allegedly provides no "correlation between…ADAM 12-L…and any disease including preeclampsia" (Office action at page 5). Additionally, the Office Action asserts that "neither the specification nor the art has identified…SEQ ID NO: 8 to correlate with preeclampsia or any related diseases." (Office Action at page 6).

Without conceding to the correctness of the Office Action assertions and solely to expedite prosecution, new claims 65-72 omit reference to ADAM 12-L and SEQ ID NO: 8 and instead recite markers related to SEQ ID NO: 3 and SEQ ID NO: 4 (ADAM 12-S).

C. ADAM 12-S as a marker for preeclampsia and related diseases

The Office Action asserts that in general, ADAM 12-S would not be a suitable marker for preeclampsia for the following reasons: (i) ADAM 12-S is detectable in blood serum during pregnancy, while it is undetectable in non-pregnancy serum; thus it is a marker for pregnancy rather than for preeclampsia; (ii) U.S. Patent Publication No. 2008/0292619 teaches that the concentration of ADAM 12-S in serum from pregnant women increases with the number of months of pregnancy; consequently, ADAM 12S would only indicate late pregnancy; (iii) Laigaard *et al.*, described that in Down Syndrome pregnancies, the concentration of ADAM 12 is decreased during the first trimester of pregnancy (Laigaard *et al.*, Prenat Diagn (2003) 23:1086-1091). Thus, the Office Action asserts that it would not be clear to the person skilled in the art how to determine whether ADAM 12 is a marker for Down Syndrome or preeclampsia in the early stages of pregnancy.

With respect to (i) and (ii), the claims recite a comparison step, in which the determined amount of the ADAM 12-S marker is compared with the amount of ADAM 12-S marker in a gestation age-matched healthy woman. By comparing the samples, the effects of the duration of pregnancy on the expression of ADAM 12-S levels is excluded from the analysis.

With respect to (iii), low levels of ADAM 12-S during the first trimester of pregnancy may be a suitable indicator for the presence of Down Syndrome; however, this does not exclude increased levels of ADAM 12-S in the second and third trimesters of pregnancy as indicative of a woman with preeclampsia or at increased risk of eclampsia, pregnancy induced hypertension, HELLP syndrome, and intrauterine growth retardation.

D. Sampling

The Office Action asserts that the specification fails to show a correlation between ADAM 12 protein levels and preeclampsia in any sample obtained from fetus, father or mother, except for maternal blood.

The Applicants respectfully point out that increased expression levels of ADAM 12-S RNA are shown in preeclamptic placental tissue as compared to control placental tissue in Figures 1 and 2. And, although an increase in RNA level is not an increase in protein level *per se*, one skilled in the art would reasonably correlate an increase in RNA levels to a subsequent increase in protein levels, and would reasonably believe that an increase in RNA levels is indicative of an increase in protein levels.

Additionally, Example 11 teaches that mRNA of placental origin is readily detectable in the maternal plasma (*see e.g.*, Ng, *et al*, PNAS (2003) 100: 4748-4753), and Example 13 showing that ADAM 12-S protein can be detected by Western Blot Analysis in blood sera of patients. Therefore, there is no doubt that ADAM 12-S RNA or protein is readily detectable in the serum or plasma of a second or third-trimester preeclamptic mother or in the placental tissue.

It is also respectfully pointed out that either ADAM 12-S protein or ADAM 12-S nucleic acid is recited as the "target" in independent claims 65 and 69. Thus, the subject matter of new claims 65-72 is fully enabled by the specification.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

V. Claim rejection – 35 U.S.C. § 112, first paragraph, written description

Claims 29-31 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to meet the written description requirement. Specifically, the Office Action asserts that "there is no described or art-recognized correlation or relationship between the structure of the invention, the ADAM 12-L or any ADAM 12 fragments including SEQ ID NO: 8 and its preeclampsia marker function," and that "one of skill in the art would not envisage…the claimed genus of peptide …which sequence as presented in SEQ ID NO: 2, any amino acid exhibiting a sequence identity with SEQ ID NO: 2 or 4 of at least 85% over 100 amino acid residues or a fragment of any of the sequences defined above which is at least 5 amino acids in length, or SEQ ID NO: 8, or the level of ligand or nucleic acid." (Office Action at page 7). The Office Action continues, "Applicant has disclosed only increase in amino acid of SEQ ID NO: 4 level in the sera for patients diagnosed with preeclampsia; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims." (Id.). The Applicants respectfully traverse this ground for rejection.

Without conceding to the correctness of the Office Action assertion and solely to expedite prosecution, claims 29-31 have been canceled, thereby obviating the rejection. New claims 65-72 meet the written description requirements of 35 U.S.C. § 112, first paragraph for at least the following reasons.

The new claims omit reference to SEQ ID NO: 8 and ADAM 12-L and instead refer to ADAM 12-S (SEQ ID NO: 3 and 4). Reference to an amino acid sequences which is at least 85% identical over 100 amino acids has also been omitted and replaced with reference to amino acid sequences with at least 95% identity to SEQ ID NO: 4 over 100 amino acid residues. Additionally, the claims recite nucleic acids encoding these proteins.

Accordingly, new claims 65-72 meet the requirements of 35 U.S.C. § 112, first paragraph, and reconsideration and withdrawal of the rejection is respectfully requested.

VI. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, the Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: May 11, 2009

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EXHIBIT
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AAFP

American Family Physician
A peer-reviewed journal of the American Academy of Family Physicians July 15, 2002

Practice Guidelines

ACOG Practice Bulletin on Diagnosing and Managing Preeclampsia and Eclampsia

Barrett M. Schroeder

The Committee on Practice BulletinsObstetrics of the American College of Obstetricians and Gynecologists (ACOG) has developed a practice bulletin on the diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin No. 33 appears in the January 2002 issue of *Obstetrics and Gynecology.*

Diagnosis

Although they have not been substantiated by research, the diagnostic criteria for preeclampsia developed by the National Blood Pressure Education Program Working Group are traditionally used in clinical practice and frequently employed in research protocols. They are as follows:

- A systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher occurring after 20 weeks of gestation in a woman whose blood pressure has previously been normal;
- Proteinuria, with excretion of 0.3 g or more of protein in a 24-hour urine specimen.

Although the exact incidence of preeclampsia remains unknown, this pregnancy-specific syndrome has been reported to affect 5 to 8 percent of pregnancies. Primarily a disorder of first pregnancies, it also occurs in many other settings, including multifetal gestations, chronic hypertension, and

pregestational diabetes.

Severe preeclampsia is diagnosed by the presence of one or more of the following:

- A systolic blood pressure of 160 mm Hg or higher or a diastolic blood pressure of 110 mm Hg or higher on two occasions six or more hours apart in a pregnant woman who is on bed rest;
- Proteinuria, with excretion of 5 g or more of protein in a 24-hour urine specimen or 3+ or greater on two random samples collected four or more hours apart;
- Oliguria, with excretion of less than 500 mL of urine in 24 hours;
- Pulmonary edema or cyanosis;
- Impairment of liver function;
- Visual or cerebral disturbances;
- Pain in the epigastric area or right upper quadrant;
- Decreased platelet count;
- Intrauterine growth restriction.

A woman with preeclampsia who has new-onset grand mal seizures is considered to have eclampsia.

Pathophysiologic Changes

Vascular changes in preeclampsia and eclampsia include hemoconcentration and intense vasospasm. Women with severe preeclampsia and liver involvement may develop HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts), which increases the risk of adverse maternal and fetal outcomes. Persistent oliguria from acute tubular necrosis can result in acute renal failure. Maternal mortality is usually associated with intracranial hemorrhage.

In addition to fetal growth restriction, manifestations of eclampsia in the fetal-placental unit include placental abruption, oligohydramnios, and nonreassuring fetal status.

Clinical Considerations and Recommendations

Is there an effective test for identifying women at risk for preeclampsia? To date, no test has been shown to be reliable and cost-effective. The positive predictive value of uric acid levels is only 33 percent. Usefulness has not been demonstrated for Doppler velocimetry of the uterine arteries in low-risk pregnant women.

How should blood pressure be measured? For accuracy, use of a mercury sphygmomanometer is preferred, and cuff size should be appropriate. Blood pressure is measured after a rest period of 10 minutes or more, with the pregnant woman in an upright position. In the hospital setting, blood pressure can be measured with the woman sitting up or lying on her left side with her arm at the level of her heart. The woman should not use tobacco or caffeine within 30 minutes of the measurement.

What is the best treatment for preeclampsia? If the fetus is preterm and preeclampsia is mild, continued fetal and maternal evaluation is appropriate. The best tests for fetal evaluation have not been determined. The Working Group recommends weekly nonstress tests and/or biophysical profiles (repeated as indicated based on the woman's condition), twice-weekly testing if oligohydramnios or fetal growth restriction is suspected, and ultrasound examinations every three

weeks. Daily assessment of fetal movement may be useful.

Laboratory tests for patients with mild preeclampsia and no progression include weekly platelet counts, liver enzyme levels, renal function evaluations, and protein levels (12- to 24-hour urine collection). If disease progression is in question, testing should be more frequent.

Pregnant women who are remote from term and have severe preeclampsia are best managed in a tertiary care center or in consultation with an obstetrician-gynecologist who has expertise in managing high-risk pregnancies. Daily laboratory tests and fetal surveillance may be needed.

Delivery in women with HELLP syndrome, regardless of gestational age, appears reasonable because of the seriousness of the syndrome. Before 32 weeks of gestation, women with HELLP syndrome should receive expectant management only in a tertiary care center or, with appropriate safeguards and informed consent, as part of a randomized clinical trial.

Is outpatient management appropriate? The Working Group reports that hospitalization is frequently recommended for women with new-onset preeclampsia. After serial assessment, the setting for continued management can be determined. Hospitalization until delivery allows rapid intervention for complications.

Ambulatory management may be an option in women with mild gestational hypertension or preeclampsia who are remote from term. In these situations, frequent monitoring is required, and hospitalization is indicated if preeclampsia worsens. If compliance is a problem, women with disease progression or severe preeclampsia should be hospitalized.

Is medical management beneficial during labor and delivery? Significant evidence supports the use of magnesium sulfate to prevent seizures in women with severe preeclampsia and eclampsia. Antihypertensive drug therapy, most commonly with hydralazine or labetalol, is generally recommended for women with a diastolic pressure of 105 to 110 mm Hg (or higher). Hydralazine is given intravenously in 5-mg to 10-mg doses until the desired response is achieved. Labetalol is given as a 20-mg intravenous bolus, followed by 40 mg after 10 minutes if the first dose is not effective; then 80 mg is administered every 10 minutes (maximum total dose: 220 mg).

What is the best delivery method in women with preeclampsia? Vaginal delivery at term is preferred in women with mild preeclampsia. The optimal delivery method in women with severe preeclampsia or eclampsia has not been evaluated. Use of cesarean delivery should be individualized.

Can anesthesia be used during labor and delivery? If required and in the absence of coagulopathy, regional or neuraxial analgesia/anesthesia is preferred.

How should eclampsia be managed? Magnesium sulfate should be given intravenously or intramuscularly to control convulsions and prevent recurrence. According to one protocol, a 4-g to 6-g loading dose diluted in 100 mL of fluid is given intravenously for 15 to 20 minutes; then a continuous intravenous infusion is administered at a rate of 2 g per hour.

Maternal treatment usually manages the fetal bradycardia that often occurs during eclampsia. Delivery should be timely, but cesarean section is not necessary. After the patient has been stabilized, the method of delivery depends on various factors, including dilation of the cervix,

gestational age, and fetal presentation.

Does invasive hemodynamic monitoring have a role in management? Invasive hemodynamic monitoring (e.g., pulmonary artery catheter) may be useful in women with preeclampsia who have severe cardiac or renal disease, pulmonary edema, treatment-refractory hypertension, or unexplained oliguria.

Can preeclampsia and eclampsia be prevented? Antioxidant therapy (vitamin C, 1,000 mg per day; vitamin E, 400 mg per day) has shown promise, but large, randomized trials are needed. Although controversy exists, calcium supplementation has shown no benefit in large trials, and most evidence suggests little or no benefit for low-dose aspirin as prevention in women in the low-risk category.

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BMC Medicine

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Commentary

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Proteinuria as a predictor of complications of pre-eclampsia

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Abstract

Proteinuria is a defining criterion for the diagnosis of pre-eclampsia. The amount of protein lost per day has been thought by some to predict both maternal and fetal outcome. The systematic review of 16 primary papers including over 6700 patients by Thangaratinam and colleagues published this month in BMC Medicine suggests otherwise. This finding may influence our management of pre-eclampsia.

Commentary

Proteinuria has been proposed and studied as both an indicator of severity of disease and as a predictor of outcome in pre-eclampsia. Many clinicians still make major management decisions based on the degree of proteinuria in such patients. The systematic review by Thangaratinam and colleagues [1] published this month in BMC Medicine suggests however that proteinuria is a poor predictor of either maternal or fetal complications in women with pre-eclampsia, and provides information that may have significant clinical implications.

Pre-eclampsia affects 2 to 3% of all pregnancies and is responsible for about 60,000 maternal deaths every year, mainly in poor countries [2]. Annually only 10 of these deaths occur in the UK [3], approximately 40 to 50 in the USA [4], while in comparison more than 200 occur in South Africa [5]. The only known cure for pre-eclampsia is delivery of the placenta. This creates a conflict of interest between the individuals on either side of the placenta: the mother stands to benefit from early delivery, while the baby may suffer complications of prematurity if born too early. Conservative management of pre-eclampsia to gain time for the baby to mature inevitably places the mother at risk [6]. Pre-eclampsia is usually a progressive disease, but the rate of progression and the occurrence of catastrophic complications such as eclampsia, cerebrovascular accident, severe HELLP syndrome, pulmonary edema or renal failure are difficult to predict. Any marker which could reliably predict the likelihood of serious complications would be very valuable for helping choose the optimal time for delivery.

Proteinuria is a defining dysfunction of pre-eclampsia [7]. Quantitation of a timed collection has been the gold standard for many decades and is expressed as the amount of protein excreted in the urine per unit time. Twenty-four-hour specimens have been traditionally used, but more recently 12-hour collections (and even 2-hour collections) have been validated [8]. The urinary protein:creatinine ratio is used in some institutions instead of a timed protein collection [9], with some finding it to be equally useful in determining pathologic proteinuria with the advantage of not requiring a timed collection, while others have not been as confident [10]. A 24-hour collection remains the standard of care in the USA [7].

The severity of the proteinuria in pre-eclampsia has been regarded by some as a predictor of adverse outcomes for the mother [11]. Others have been less sanguine about the relationship [12]. A reliable correlation between the level of proteinuria and severity of pre-eclamptic complications would be extremely valuable for clinical decision making.

The review by Thangaratinam et al [1] reported in this issue sets a new standard for systematically searching for, evaluating and aggregating the results of studies of this kind. The results are disappointing in that the correlation found between level of proteinuria and severity of clinical disease was insufficiently reliable to be clinically useful. The authors reported that from a fetal point of view, the only statistically significant findings were that proteinuria of 5 g/24 h in a timed specimen, or 1+ and 3+ in a dipstick specimen, predicted stillbirth with a likelihood ratio for the positive result of 1.3 to 2.3 ('little useful' to 'somewhat useful'). Maternal outcomes fared equally poorly. The same group of authors has previously reported on another biochemical marker, serum urate, with similarly disappointing results [13].

Despite the rigor and efforts to determine the quality of the studies included in the current review, practice differences, equipment changes, and definitions of pre-eclampsia could have influenced the diagnosis (and management) of pre-eclampsia over the time period of the studies used. Thirty years ago changes in systolic pressure and diastolic pressure during gestation were being used to define pre-eclampsia (the so-called 30/15 rule) and if the diagnosis of pre-eclampsia is differently defined in different studies the validity of the result may be diminished.

A very important potential confounding factor to consider in studies of the kind reviewed, is that the test result (in this case severe proteinuria), particularly in the earlier studies, may have dictated management. In the USA at least, proteinuria of 5 g or more per 24 hours is one of the diagnostic criteria for severe pre-eclampsia [7]. If women were delivered earlier as a result of a positive test for severe proteinuria then that test cannot be stated to have been used to predict outcome, since its result was used to intervene and thus influence the outcome. Earlier delivery precipitated by a positive test result may, for example, reduce maternal complications (leading to an underestimation of the predictive value of the test), or increase perinatal morbidity due to prematurity, leading to an overestimation. The test would technically have an association with the outcome, rather than a predictive capability.

Despite these limitations, this metanalysis appears to confirm what clinicians have suspected for a long time. The degree of proteinuria alone does not have a strong association with adverse outcome. Maternal and fetal clinical condition and gestational age, complemented by hematologic and biochemical parameters, should for the time being remain the primary determinants for timing delivery in women with pre-eclampsia.

As the results of observational studies may systematically over- or underestimate the predictive value of tests as discussed above, a randomized trial of knowledge versus no knowledge of the level of proteinuria to guide management would be justified.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MAB and GJH drafted the manuscript and MAB revised it for important intellectual content. MAB and GJH have both given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for the content.

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SECTION Gynecology and Obstetrics

SUBJECT Abnormalities of Pregnancy

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Preeclampsia and Eclampsia

Preeclampsia *is pregnancy-induced hypertension plus proteinuria.* ***Eclampsia*** *is unexplained generalized seizures in patients with preeclampsia. Preeclampsia and eclampsia develop between 20 wk gestation and the end of the 1st wk postpartum. Diagnosis is clinical and by urine protein measurement. Treatment is with IV Mg sulfate and usually rapid delivery.*

Preeclampsia affects 3 to 7% of pregnant women, usually primigravidas and women with preexisting hypertension (see Pregnancy Complicated by Disease: Hypertension in Pregnancy) or vascular disorders (eg, renal disorders, diabetic vasculopathy). Other risk factors may include maternal age < 20, a family history of preeclampsia, preeclampsia or poor outcome in previous pregnancies, multifetal pregnancy, obesity, and thrombotic disorders (eg, antiphospholipid antibody syndrome—see Thrombotic Disorders: Antiphospholipid Antibody Syndrome).

Preeclampsia develops during pregnancy and eclampsia usually does, but 25% of eclampsia cases develop postpartum, most often in the 1st 4 days. Untreated preeclampsia usually smolders for a variable time, then suddenly progresses to eclampsia,

which occurs in 1/200 patients with preeclampsia. Untreated eclampsia is usually fatal.

Etiology

Cause and pathophysiology of preeclampsia and eclampsia are unknown. Factors may include poorly developed uterine placental spiral arterioles (which decrease uteroplacental blood flow in late pregnancy) and placental ischemia or infarction. Fetal growth restriction may result. Diffuse or multifocal vasospasm can result in ischemia, eventually damaging multiple organs, particularly the brain, kidneys, and liver. Contributors to vasospasm may include decreased prostacyclin (an endothelium-derived vasodilator), increased endothelin (an endothelium-derived vasoconstrictor), and increased soluble Flt-1 (a circulating receptor for vascular endothelial growth factor).

Lipid peroxidation of cell membranes induced by free radicals may contribute to preeclampsia. The coagulation system is activated, possibly secondary to endothelial cell dysfunction, leading to platelet activation. However, frank coagulopathy is rare unless abruptio placentae is also present.

Symptoms and Signs

Preeclampsia may be asymptomatic or may cause edema or excessive weight gain. Nondependent edema such as facial or hand swelling (the patient's ring may no longer fit her finger) is more specific than dependent edema. Other signs may include increased reflex reactivity, indicating neuromuscular irritability, which can progress to seizures (eclampsia). Petechiae may reflect a bleeding tendency. Severe preeclampsia may cause organ damage; manifestations may include headache, visual disturbances, confusion, epigastric or right upper quadrant abdominal pain (reflecting hepatic ischemia or capsular enlargement), nausea, vomiting, shortness of breath or dyspnea (reflecting pulmonary edema or acute respiratory distress syndrome [ARDS]), and oliguria (reflecting decreased plasma volume or ischemic acute tubular necrosis).

Diagnosis

Diagnosis is suggested by symptoms or presence of hypertension. Tests include urinalysis, CBC, platelet count, urate, liver function tests, and measurement of serum electrolytes, BUN, creatinine, creatine clearance, and 24-h urine protein. Preeclampsia is diagnosed when pregnant women have new-onset hypertension (BP $\geq$ 140/90 mm Hg) plus unexplained proteinuria of $\geq$ 1+ on dipstick on 2 occasions at least 4 h apart after 20 wk. Occasionally, tests detect the HELLP syndrome (*h*emolysis, *e*levated *l*iver function tests, and *l*ow *p*latelets).

Preeclampsia is classified as severe based on symptoms; other evidence of organ damage; presence of fetal growth restriction; and laboratory tests, including results that indicate HELLP syndrome, BP ≥ 160/110 mm Hg on 2 occasions ≥ 6 h apart, urine protein ≥ 5 g in a 24-h collection or ≥ 3+ in 2 samples obtained ≥ 4 h apart, and urine output < 500 mL in 24 h.

Treatment

Definitive treatment is delivery. For term pregnancy, immediate delivery after maternal stabilization is safest. For pregnancies < 37 wk, risk of early delivery is balanced against severity of the preeclampsia and response to treatment. Treatment aims to optimize maternal health, which usually optimizes fetal health. If preeclampsia is mild, outpatient treatment is possible; it includes strict bed rest, lying on the left side whenever possible, a normal salt intake, increased fluid intake, and evaluation every 2 or 3 days.

Patients with mild eclampsia that does not immediately abate, severe preeclampsia, or eclampsia require hospitalization; a few hours of stabilizing medical treatment to lower BP to 140 to 155/90 to 105 mm Hg, and to resolve seizures and reduce reflex reactivity; and then delivery. Exceptions include advanced prematurity when mild preeclampsia does not progress and severe preeclampsia that improves with hospitalization. Whether patients with mild preeclampsia always require Mg sulfate before delivery is controversial. Patients with severe preeclampsia require Mg sulfate as soon as diagnosis is made. When delivery is delayed before about 32 to 34 wk in patients who are not clinically deteriorating, corticosteroids are given for 48 h. Delivery is mandated at 34 wk or when deterioration of maternal or fetal status or documentation of fetal lung maturity occurs. Eclampsia always requires delivery after seizures and severe hypertension have been controlled. All hospitalized patients are checked frequently for seizures, symptoms of severe preeclampsia, and vaginal bleeding. BP, reflexes, and fetal heart rate are monitored continuously or several times a day.

Patients with severe preeclampsia or with eclampsia are often admitted to the ICU. Continued management by the obstetrician is mandatory. As part of stabilization, these patients are given IV Ringer's lactate or 0.9% normal saline solution at about 125 mL/h (to increase urine output) and IV Mg sulfate (to stop or prevent seizures and reduce reflex reactivity and BP). Mg sulfate 4 g IV over 20 min is followed by a constant IV infusion of about 1 to 3 g/h, with supplemental doses as necessary. Dose is adjusted based on the patient's reflexes, BP, and serum Mg levels (therapeutic range, 4 to 7 mEq/L). Patients with excess Mg levels (eg, with Mg levels > 10 mEq/L or a sudden decrease in reflex reactivity)

or hypoventilation are treated with Ca gluconate 1 g IV. IV Mg sulfate may cause lethargy, hypotonia, and transient respiratory depression in neonates. However, serious neonatal complications are uncommon.

If Mg therapy is ineffective, phenytoin or valium can be given to stop seizures, and IV hydralazine or labetalol is given in a titrated dose to lower BP to 140 to 155/90 to 105 mm Hg. Persistent oliguria is treated with a fluid challenge, followed by furosemide 10 to 20 mg IV; *diuretics are not used otherwise*. If fluids plus furosemide are ineffective, determining intravascular volume and cardiac output with a Swan-Ganz catheter may be considered. Anuric patients with normovolemia may require renal vasodilators or dialysis.

The most efficient method of delivery should be used. If the cervix is favorable and rapid vaginal delivery seems feasible, a dilute IV infusion of oxytocin is given to accelerate labor; if labor is active, the membranes are ruptured. If the cervix is unfavorable and prompt vaginal delivery is unlikely, delivery by cesarean section is indicated. Preeclampsia and eclampsia, if not resolved before delivery, usually resolve rapidly afterward, beginning within 6 to 12 h. As patients gradually improve, ambulation is allowed. Patients should be evaluated every 1 to 2 wk postpartum with periodic BP measurement. If BP remains high after 8 wk postpartum, chronic hypertension should be considered.

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